Variation in Influenza B Virus Epidemiology by Lineage, China

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We used national sentinel surveillance data in China for 2005–2016 to examine the lineage-specific epidemiology of influenza B. Influenza B viruses circulated every year with relatively lower activity than influenza A. B/Yamagata was more frequently detected in adults than in children.

Influenza B virus, first identified in 1940 (*1*), is associated with considerable hospital admissions and deaths worldwide every year (*2*). During the early 1980s, influenza B viruses split into 2 lineages, termed B/Victoria and B/Yamagata (*3*). These 2 lineages showed distinct antigenicity and transmission dynamics (*4*) and have co-circulated during each influenza season since 2001 (*2*). Relatively less attention has been given to influenza B virus epidemiology than to influenza A epidemiology (*2*) because influenza B virus spreads almost exclusively in humans and does not pose a pandemic threat (*5*).

Several recent reports have highlighted potential differences in the epidemiology of B/Victoria and B/Yamagata lineage viruses, including younger average ages of persons with B/Victoria virus infection (*4*,*6*,*7*) and greater transmissibility of B/Victoria viruses (*4*,*6*). Our study aimed to describe epidemiologic patterns of influenza B virus activity in China and to identify and compare the seasonality and age distribution of persons with medically attended influenza B/Victoria and B/Yamagata virus infections.

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The Study

The Chinese Center for Disease Control and Prevention coordinated influenza surveillance in sentinel clinics during October 2005–March 2016. Sentinel hospitals in provinces in southern China conducted year-round surveillance; in northern China (except for Liaoning, Gansu, and Tianjin provinces, where year-round surveillance was conducted), surveillance was suspended from April to September before 2009 because influenza has low activity in summer in these temperate areas of China (*8*). Sentinel surveillance was then expanded from 193 to 554 hospitals conducting year-round surveillance in all provinces since 2009. Sentinel hospitals reported the number of outpatients and the number of outpatients with influenza-like illness symptoms on a daily basis. Respiratory specimens collected from a subset of outpatients with influenza-like illness were tested for influenza viruses. Each sentinel hospital in northern China was required to collect 10–15 samples per week during October–March and 5–15 samples per month during April–September for virus testing, and the hospitals in southern China tested 5–15 samples per week throughout the year. Most laboratories had adopted real-time PCR for lineage identification since 2009; some laboratories still use virus culture followed by hemagglutination inhibition test (online Technical Appendix, https://wwwnc.cdc.gov/EID/article/24/8/18-0063-Techapp1.pdf). Individual data on age, sex, and date of specimen collection also were reported for all selected patients for virus testing (online Technical Appendix). Because national influenza sentinel surveillance was part of a routine public health investigation, the study was exempt from institutional review board assessment, and all data were delinked from identifiable personal information.

We used a proxy measure of influenza activity in the communities served by the sentinel locations because it was previously indicated to be a good correlate of the incidence rates of influenza virus infection in the community (*9*). The proxy was calculated as the product of the weekly rates for influenza-like illness consultation and the proportion of sentinel specimens testing positive for each lineage in the same week. The age-specific proportions of sentinel

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specimens testing positive for influenza B virus by lineage were derived as the proportion of sentinel specimens testing positive for each lineage (numerator) among the outpatients recruited for specimen collection (denominator) by exact year of age.

We found that influenza B/Victoria and B/Yamagata lineages circulated every year in mainland China during 2005–2016 and were mostly active during the winter–spring seasons (Figure 1). Influenza B virus activity was generally less intense than influenza A activity and less apparent during the 2005–06, 2010–11, and, particularly, 2012–13 seasons (Figure 1; online Technical Appendix Figure 1).

Influenza B/Victoria activity increased in every season before and during the first wave of infections with influenza A(H1N1)pdm09 virus in China in late 2009, whereas substantial virus detections were only seen in the early 2011–12 and 2015–16 seasons during the postpandemic period. B/Yamagata lineage led to 3 major epidemics during the 2007–08, 2013–14, and 2014–15 seasons (online Technical Appendix Figure 1). These major epidemics were associated with prolonged influenza activity, particularly during summer periods and in provinces and municipalities with lower latitude, which occurred during 2008–2011 for B/Victoria lineage and during the 2007–08 and 2014–15 seasons for B/Yamagata lineage (Figure 1).

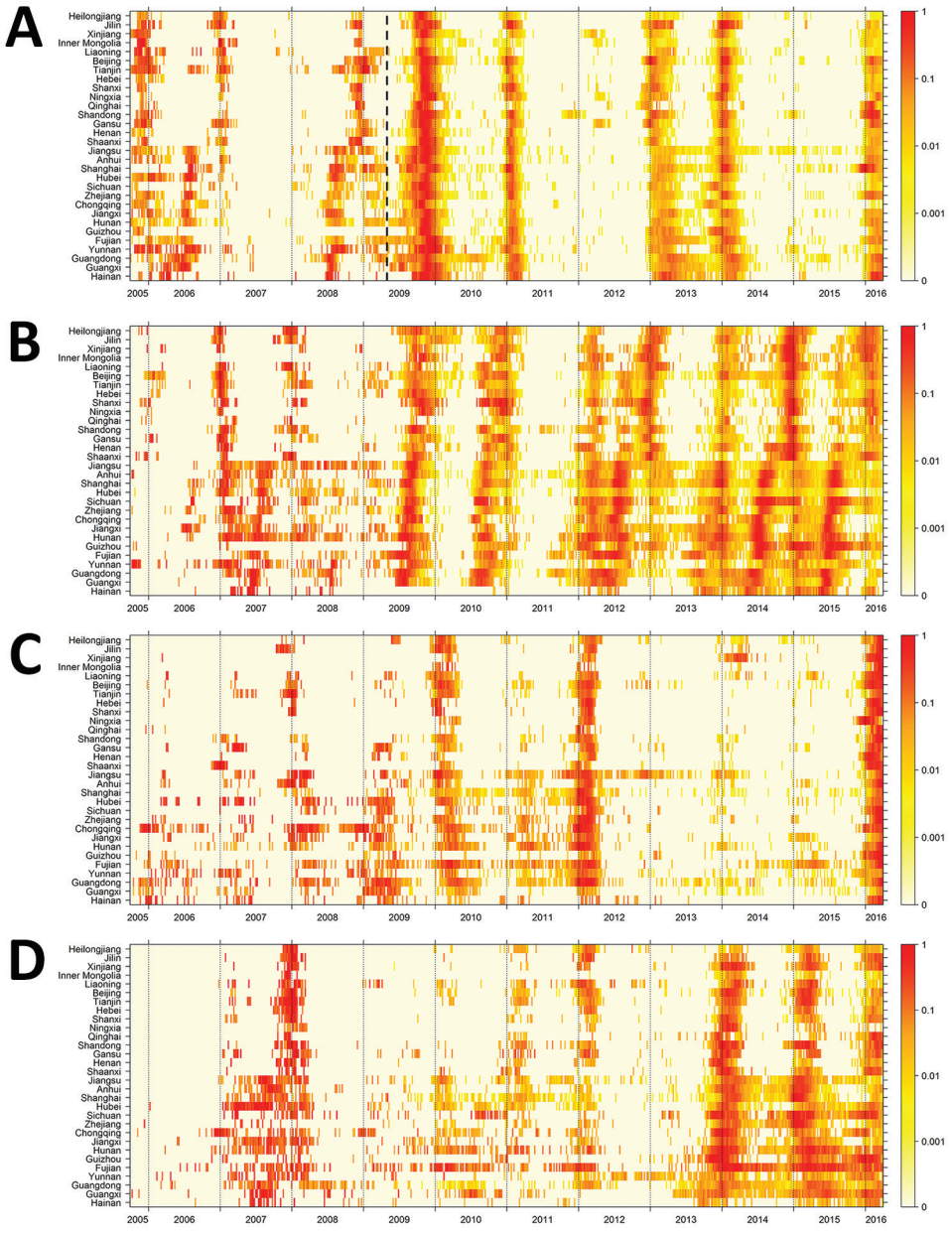

Figure 1. Heatmap of influenza virus activity by lineage in 30 provinces and municipalities (sorted by latitude), China, October 2005–March 2016. A) Influenza A(H1N1); B) influenza A(H3N2); C) influenza B/Victoria lineage; D) influenza B/Yamagata lineage. Map is based on 2,498,735 specimens collected from the sentinel hospitals. Normalized virus activity is shown for each province and municipality as the product of the weekly proportion of influenza-like illness consultations and the weekly proportion of sentinel specimens testing positive for influenza viruses divided by the maximum virus activity in the province or municipality throughout the study period to give a rescaled proxy with values between 0 (no activity) and 1 (highest activity in that province). The dashed line in panel A indicates the start of the H1N1 pandemic in 2009.

Children 5–15 years of age had the highest detection rates among all age groups for both lineages. The rates of detection of B/Victoria lineage viruses decreased with age after peaking at 10 years of age, and the rates of B/Yamagata lineage virus infections generally increased among persons >25 years of age to a second peak in older adults (Figure 2, panel A). The patterns differed somewhat across provinces and municipalities without systematic variation by latitude (online Technical Appendix Figure 2). In comparison, influenza A(H1N1) showed an age pattern similar to that for B/Victoria but with a later peak, at 10–20 years of age; however, influenza A(H3N2) indicated largely comparable virus detections across different age groups (Figure 2, panel B).

Conclusions

Our study showed that influenza B virus generally was relatively less active than influenza A virus (Figure 1; online Technical Appendix Figure 1). Influenza B/Yamagata caused fewer epidemics than B/Victoria during the study period, largely consistent with findings from a study using sentinel surveillance data from multiple countries (*10*). The alternating predominance of the B/Victoria and B/Yamagata lineages, especially after 2009, and the low influenza B virus activity in China during the 2012–13 season might reflect the complex interactions between population immunity and virus evolution of influenza B lineages (*11*).

Our study suggested a potential difference in the age patterns of persons infected with B/Yamagata and

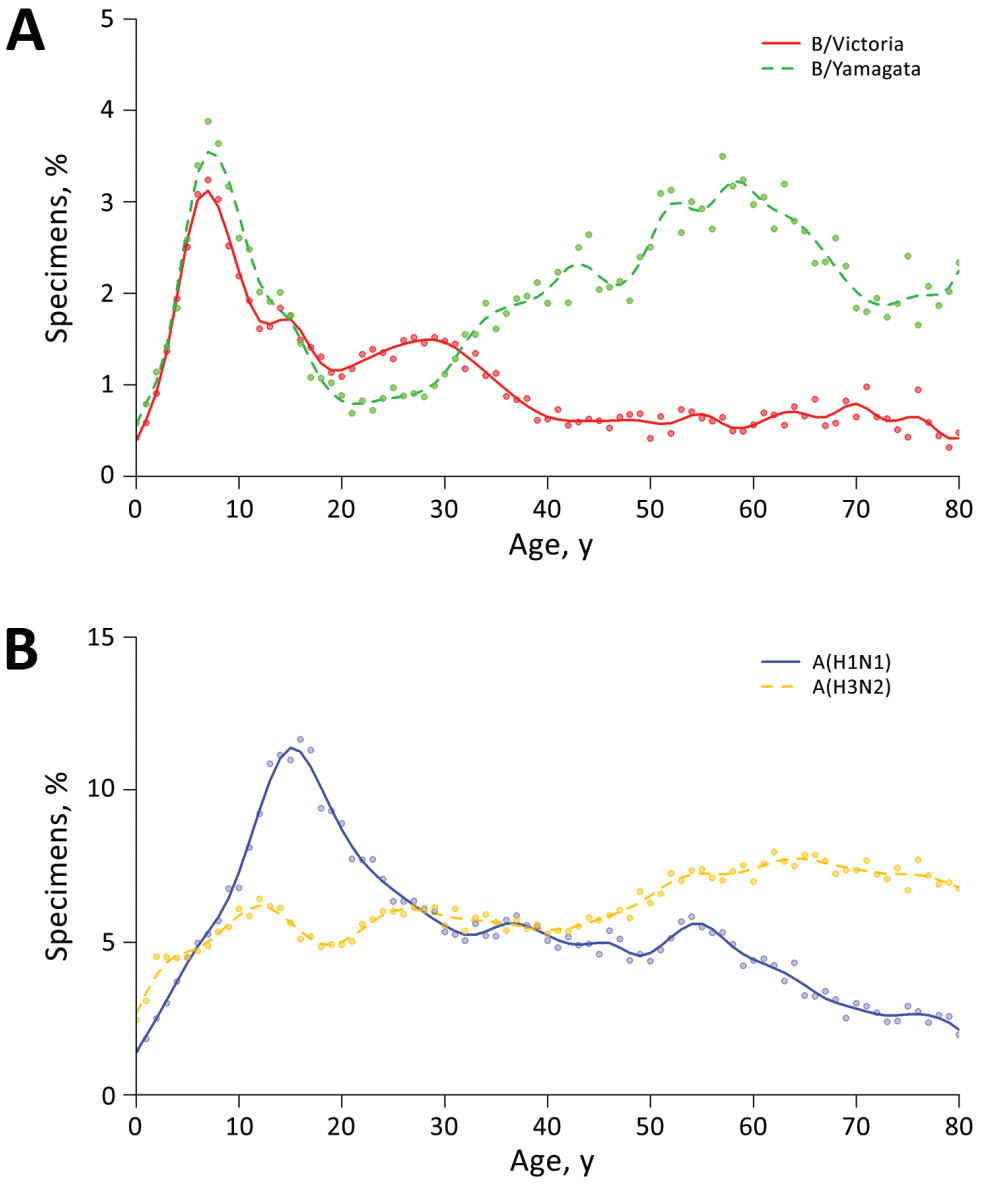

Figure 2. Age-specific proportions of sentinel specimens collected from sentinel surveillance sites testing positive for influenza, China, October 2005–March 2016. A) Influenza B/Victoria and B/Yamagata lineages; B) influenza A(H1N1) and A(H3N2). Findings are based on 2,498,735 specimens collected from the sentinel hospitals. Dots indicate the original data, and lines (solid and dashed) show the estimation from a fitted smoothing function to the pattern by age.

B/Victoria (Figure 2). The elevated proportions of infections with both lineages in children might indicate a lack of exposure to the virus early in life (*4*,*12*). However, the discrepancy in susceptibility to infections with B/Victoria and B/Yamagata in older adults might reflect the genetic difference in viruses of the 2 lineages, although previous exposure to different lineages and vaccination history might have had an effect. Antigenic analysis indicated that circulating B/Yamagata strains in general showed a larger genetic diversity than B/Victoria strains (*4*). This genetic diversity may lead to a substantial number of persons infected with a certain strain of B/Yamagata virus who are susceptible to the other co-circulating strains of the same lineage. The declining frequency of B/Victoria detections with age, however, implied a gradually strengthened immunity in older persons, which could be attributed to accumulated immunity from exposure to virus strains with fewer genetic changes or possibly to the boosted heterologous immunity against B/Victoria viruses induced by exposure to B/Yamagata viruses (*13*).

The study has several limitations. First, expansion of the national sentinel surveillance system in China since 2009 might have affected the observed patterns in virus activity because of inclusion of sentinel clinics providing healthcare services specifically to certain populations, such as patients in respiratory or pediatric outpatient clinics, although we weighted virus activity by age in the analysis. Second, the wider application of PCR in national surveillance laboratories might have led to an artificial increase in virus activity; however, we assumed that this change would not differ between the 2 lineages.

Further work could examine the degree of cross-protection conferred by infections of the opposite lineage, if any (*13*,*14*). Results from such studies would further elucidate the epidemiology of influenza B virus and optimize vaccination strategies in China.

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Technical Appendix

National Influenza Sentinel Surveillance in China

The influenza sentinel surveillance in China was established in 2005 and has been substantially expanded from 193 to 554 sentinel hospitals since the 2009 influenza A(H1N1)pdm09 pandemic. The surveillance has involved multiple outpatient clinics in sentinel hospitals, including internal medicine, internal medicine emergency, pediatrics, pediatric emergency and fever clinics. The number of clinics would change over time because more sentinel hospitals have been included into the surveillance, and a small proportion of sentinel hospitals might have been removed from the surveillance system. The annual proportions of clinics involved in the surveillance are shown in Technical Appendix Table 1.

Laboratory Methods for Determining Influenza B Lineages

The national influenza sentinel surveillance in China currently comprises 560 sentinel hospitals and has been substantially expanded since the 2009 influenza A(H1N1) pandemic. The network laboratories in the surveillance system conducted virus determination according to the standard methods in the World Health Organization (WHO) protocols of the Manual for the Laboratory Diagnosis and Virological Surveillance of Influenza (*1*) and WHO Information for the Molecular Detection of Influenza Viruses (*2*).

Before the 2009 A(H1N1) pandemic, influenza B lineages were differentiated by virus culture followed by the hemagglutination-inhibition (HAI) assay with standardized antiserum. To monitor the circulating characteristics of 2 influenza B virus lineages rapidly and sensitively, real-time reverse transcription PCR (rRT-PCR) began to be used more frequently since May 2009, when the A(H1N1) pandemic occurred. Since then the laboratories in the surveillance

network have been performing either virus culture followed by HAI assay or rRT-PCR or both for lineage determination.

1. Virus Culture Followed by HAI Assay

Samples are inoculated into MDCK (ATCC CCL 34) cells and/or specific pathogen-free embryonated chicken eggs (9–11 days old) for virus isolation in biosafety level 2 facilities at the influenza surveillance network laboratories. MDCK cells were grown in Dulbecco's modified Eagle's medium (Invitrogen, Carlsbad, CA, USA) containing 10% fetal bovine serum (Invitrogen). In the HAI assays, the standardized antigen and ferret antiserum that raised against B/Yamagata and B/Victoria lineages recommended by WHO for Northern Hemisphere influenza vaccine strains were prepared by the Chinese National Influenza Center (CNIC), one of WHO's influenza reference center, following the WHO Manual for the Laboratory Diagnosis and Virological Surveillance of Influenza (*1*). The standardized antigen and ferret antiserum were provided to all influenza surveillance network laboratories by CNIC. The details of virus culture followed by HAI assay to determine influenza B lineage have been published by the authors elsewhere (*3*). The quality control and assessment for the virus isolation and lineages differentiation were operated by CNIC yearly.

2. 1-Step rRT-PCR for the Detection of Influenza B Lineage

Viral RNA was extracted using the QIAamp Viral RNA Minikit (QIAGEN, Hilden, Germany, cat.no. 52904) according to the manufacturer's instructions. One-step rRT-PCR was further used to detect influenza B type and determine lineages. The primers and probes sequence were provided by CNIC to all influenza surveillance network laboratories according to the WHO Information for the Molecular Detection of Influenza Viruses (*2*). The reaction master mixture and thermocycling conditions also was performed according to (*2*). A cycle threshold $\leq$37 was considered positive for the influenza B lineage determination. Several predominant influenza B virus strains, including B/Yamagata and B/Victoria in annual influenza epidemics, were used to validate the sensitivity of primers and probes. Several influenza A virus strains, including seasonal H1N1, pandemic H1N1, seasonal H3N2; and avian influenza H5N1, H9N2, and H7N9 (since 2013) were used to validate the specificity of the assays by CNIC yearly. The sequence of primers and probes with no cross-reactivity reactions would be provided to network laboratories

for the lineage detection. All the 1-step rRT-PCRs were performed by network laboratories. The quality control and assessment for the lineages differentiation were operated by CNIC yearly.

Technical Appendix Table 2 reports the distributions of specimens by age group, province, and testing method in each year of the study period.

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Technical Appendix Table 1. Annual proportions of clinics involved in the national influenza sentinel surveillance, China*

	Clinic					
Season	Internal medicine	Internal medicine emergency	Pediatrics	Pediatric emergency	Fever clinic	Total no. sentinel clinics
2005–06	0.249	0.213	0.301	0.165	0.071	162108
2006–07	0.246	0.212	0.296	0.163	0.084	184370
2007–08	0.243	0.209	0.297	0.165	0.085	187625
2008–09	0.232	0.205	0.276	0.154	0.132	262621
2009–10	0.220	0.206	0.245	0.140	0.188	619799
2010–11	0.225	0.209	0.248	0.139	0.180	669101
2011–12	0.225	0.210	0.247	0.143	0.176	699090
2012–13	0.223	0.210	0.247	0.145	0.175	715918
2013–14	0.223	0.209	0.246	0.145	0.177	723199
2014–15	0.222	0.210	0.246	0.147	0.175	727677
2015–16	0.221	0.210	0.246	0.149	0.175	372462

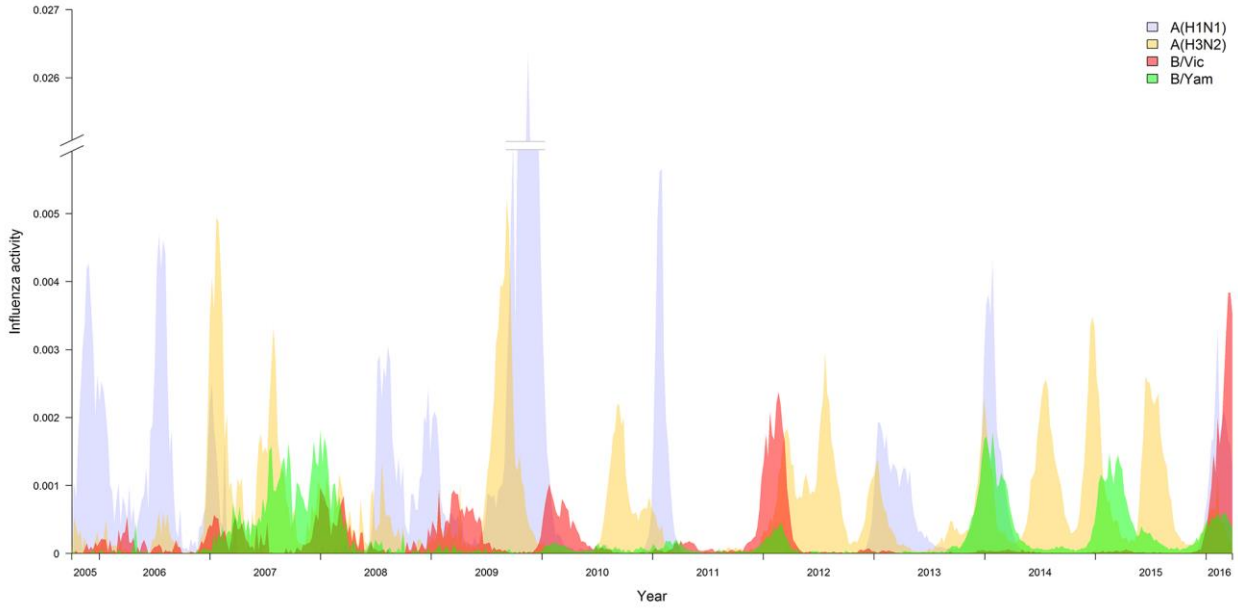
*In general, the proportions of sentinel clinics by type of clinic remained relatively stable during the study period, whereas more fever clinics have been involved in the surveillance more recently.

Technical Appendix Table 2. Distribution of sentinel specimens from sentinel surveillance hospitals and proportions of network laboratories using different testing methods in each influenza season, China

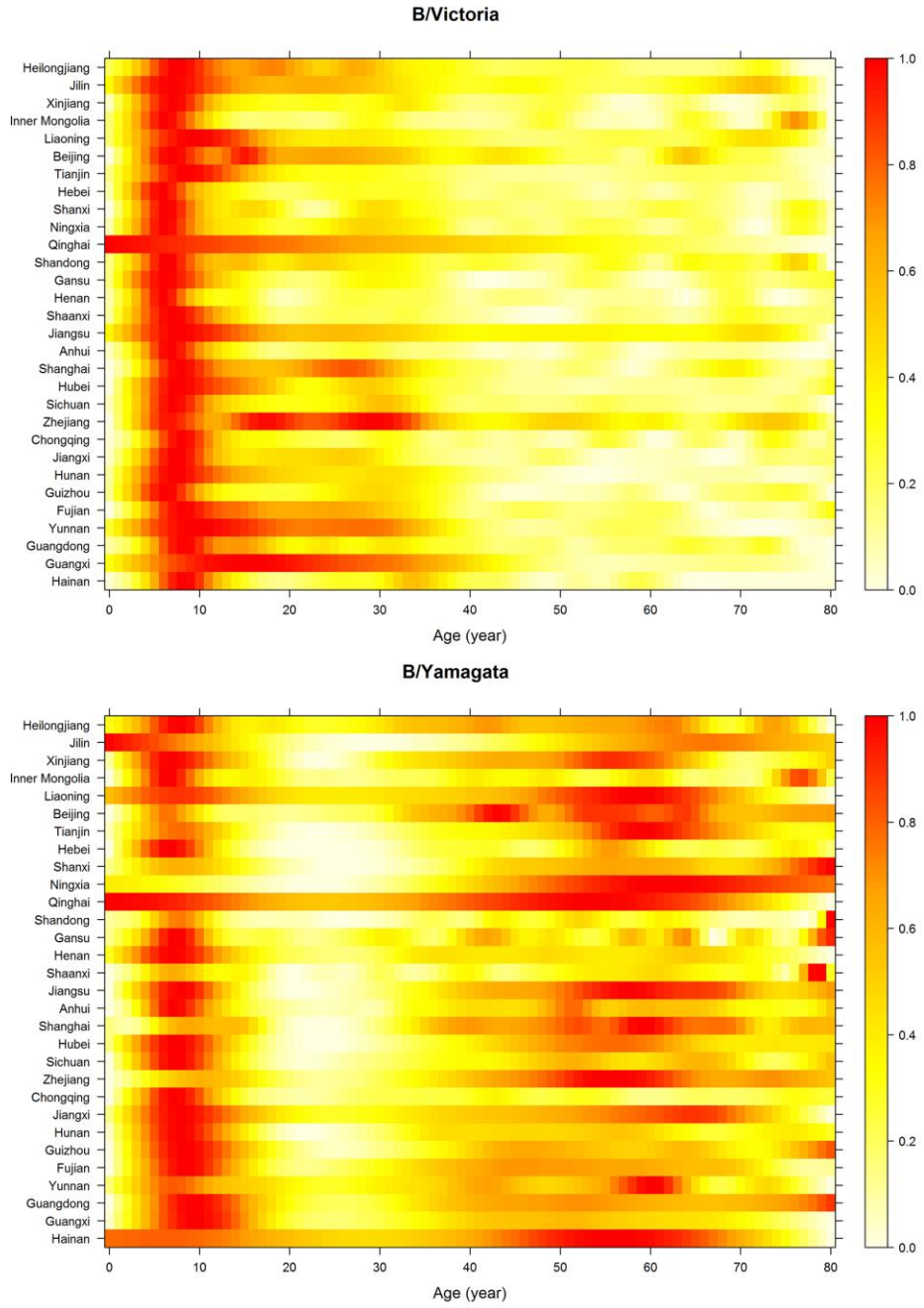
Variable	Influenza season										
	2005–06	2006–07	2007–08	2008–09	2009–10	2010–11	2011–12	2012–13	2013–14	2014–15	2015–16
Total no. specimens	37,360	39,024	41,540	141,825	321,859	201,652	219,633	301,080	442,314	462,756	289,692
Age group, y, %											
0–5	0.512	0.542	0.548	0.341	0.307	0.432	0.433	0.45	0.444	0.474	0.48
6–10	0.173	0.145	0.141	0.129	0.132	0.117	0.125	0.106	0.121	0.117	0.133
11–15	0.057	0.055	0.05	0.102	0.096	0.052	0.056	0.047	0.045	0.042	0.039
16–20	0.051	0.05	0.048	0.107	0.107	0.058	0.055	0.053	0.049	0.042	0.039
21–25	0.048	0.046	0.047	0.081	0.09	0.073	0.066	0.067	0.059	0.051	0.043
26–30	0.04	0.044	0.042	0.067	0.076	0.068	0.065	0.068	0.064	0.06	0.059
31–35	0.03	0.027	0.025	0.039	0.04	0.04	0.04	0.042	0.041	0.038	0.039
36–40	0.022	0.021	0.023	0.034	0.034	0.035	0.031	0.032	0.032	0.028	0.027
41–45	0.016	0.015	0.015	0.022	0.023	0.025	0.024	0.026	0.027	0.025	0.024
46–50	0.013	0.013	0.014	0.02	0.022	0.025	0.026	0.026	0.025	0.025	0.024
51–55	0.012	0.012	0.013	0.017	0.019	0.02	0.019	0.018	0.021	0.023	0.022
56–60	0.009	0.009	0.01	0.015	0.017	0.02	0.02	0.021	0.023	0.023	0.019
61–65	0.005	0.007	0.006	0.008	0.011	0.011	0.013	0.015	0.017	0.018	0.017
66–70	0.004	0.005	0.006	0.006	0.008	0.008	0.009	0.01	0.011	0.012	0.012
71–75	0.004	0.004	0.004	0.006	0.007	0.007	0.008	0.008	0.009	0.009	0.008
76–80	0.003	0.003	0.004	0.004	0.006	0.006	0.006	0.007	0.008	0.008	0.007
>80	0.002	0.002	0.002	0.003	0.004	0.004	0.004	0.005	0.006	0.007	0.007
Province, %											
Heilongjiang	0.01	0.016	0.022	0.028	0.025	0.033	0.039	0.031	0.032	0.03	0.039
Jilin	0.018	0.028	0.025	0.017	0.023	0.018	0.018	0.019	0.019	0.019	0.025
Xinjiang	0.019	0.014	0.014	0.022	0.037	0.04	0.032	0.028	0.029	0.028	0.039
Inner Mongolia	0.008	0.017	0.021	0.021	0.021	0.018	0.019	0.021	0.02	0.022	0.032
Liaoning	0.022	0.018	0.023	0.043	0.063	0.037	0.037	0.037	0.033	0.03	0.039
Beijing	0.026	0.016	0.017	0.032	0.033	0.035	0.049	0.037	0.027	0.025	0.02
Tianjin	0.027	0.026	0.026	0.013	0.012	0.015	0.015	0.014	0.014	0.013	0.017
Hebei	0.029	0.024	0.024	0.038	0.034	0.029	0.033	0.035	0.029	0.034	0.046
Shanxi	0.006	0.013	0.016	0.017	0.014	0.018	0.02	0.022	0.022	0.023	0.033
Ningxia	0.012	0.011	0.012	0.012	0.019	0.012	0.011	0.014	0.013	0.014	0.017
Qinghai	0.014	0.009	0.009	0.006	0.006	0.011	0.009	0.012	0.009	0.013	0.014
Shandong	0.017	0.02	0.023	0.025	0.037	0.047	0.045	0.046	0.044	0.039	0.051
Gansu	0.035	0.043	0.046	0.041	0.028	0.032	0.032	0.029	0.024	0.027	0.035
Henan	0.011	0.018	0.015	0.048	0.033	0.029	0.03	0.035	0.033	0.032	0.042
Shaanxi	0.022	0.023	0.011	0.016	0.016	0.016	0.023	0.023	0.027	0.029	0.041
Jiangsu	0.067	0.059	0.034	0.079	0.095	0.087	0.08	0.079	0.071	0.066	0.053
Anhui	0.064	0.067	0.048	0.041	0.041	0.038	0.043	0.05	0.058	0.057	0.048
Shanghai	0.014	0.031	0.029	0.027	0.048	0.049	0.057	0.044	0.044	0.043	0.034
Hubei	0.054	0.056	0.067	0.044	0.032	0.047	0.047	0.039	0.038	0.038	0.032
Sichuan	0.01	0.009	0.026	0.033	0.029	0.034	0.037	0.039	0.034	0.046	0.042
Zhejiang	0.062	0.051	0.048	0.049	0.054	0.035	0.029	0.035	0.04	0.037	0.03
Chongqing	0.04	0.022	0.039	0.019	0.015	0.014	0.017	0.017	0.014	0.013	0.011
Jiangxi	0.039	0.037	0.037	0.026	0.022	0.021	0.033	0.041	0.038	0.035	0.027
Hunan	0.063	0.085	0.079	0.067	0.05	0.044	0.038	0.043	0.055	0.055	0.048
Guizhou	0.022	0.024	0.022	0.031	0.023	0.032	0.028	0.032	0.032	0.03	0.024
Fujian	0.069	0.075	0.073	0.048	0.032	0.022	0.027	0.03	0.035	0.033	0.026

Variable	Influenza season										
	2005–06	2006–07	2007–08	2008–09	2009–10	2010–11	2011–12	2012–13	2013–14	2014–15	2015–16
Yunnan	0.045	0.054	0.041	0.028	0.028	0.051	0.042	0.03	0.037	0.049	0.039
Guangdong	0.09	0.061	0.091	0.084	0.082	0.088	0.074	0.072	0.071	0.066	0.052
Guangxi	0.07	0.054	0.045	0.026	0.034	0.032	0.025	0.033	0.044	0.04	0.033
Hainan	0.014	0.018	0.014	0.02	0.015	0.014	0.011	0.011	0.014	0.014	0.011
PCR result, %											
H1	0.321	0	0.6	0.021	0.002	0.001	0	0	0	0	0
H1N1pdm	0	0	0	0.056	0.159	0.051	0.002	0.038	0.048	0.001	0.049
H3	0	0.833	0	0.122	0.026	0.031	0.075	0.029	0.064	0.088	0.032
A(others)	0	0	0	0.063	0.02	0.006	0.006	0	0	0	0
B/Victoria	0	0	0	0.002	0.012	0.004	0.036	0.001	0.001	0.001	0.059
B/Yamagata	0	0.167	0.2	0.001	0.002	0.004	0.006	0.001	0.034	0.036	0.02
B(others)	0.226	0	0	0.012	0.055	0.025	0.067	0.002	0.013	0.005	0.016
Negative	0.452	0	0.2	0.724	0.724	0.878	0.807	0.928	0.838	0.867	0.824
Testing methods used by laboratories, %											
HAI assay	0.998	1	1	0.354	0.032	0.246	0.297	0.182	0.115	0.134	0.141
PCR	0.000	0	0	0.506	0.815	0.598	0.495	0.601	0.618	0.639	0.657
HAI assay and PCR	0.002	0	0	0.140	0.152	0.156	0.209	0.218	0.267	0.227	0.202

*Seasons defined as the start of October until the end of September of the next year. The column sum of proportions by age group, province/municipality, PCR result, and testing method = 1. The distribution of positive specimens identified by PCR by laboratories that adopted the PCR approach or both PCR and HAI assay for virus identification is shown under “PCR result,” in which A(others) showed the proportion of specimens with unsubtyped or co-infected seasonal influenza A viruses and avian influenza viruses including H5-positive, H7-positive, H9-positive; whereas B(others) showed the proportion of specimen with unsubtyped or co-infected influenza B viruses. HAI, hemagglutination-inhibition.



Technical Appendix Figure 1. National influenza virus activity by virus subtype (A(H1N1) and A(H3N2)) and lineage (B/Victoria and B/Yamagata), China, October 2005–March 2016. Findings are based on 2,498,735 specimens collected from the sentinel hospitals. Influenza activity is shown as the average of the provincial/municipal proxy, which is the product of the weekly proportion of influenza-like illness consultations and the weekly proportion of sentinel specimens testing positive for a specific type of virus, weighted by the population size of each province and municipality.



Technical Appendix Figure 2. Heatmap of the age-specific proportions of sentinel specimens testing positive for influenza B/Victoria and B/Yamagata lineages in 30 provinces and municipalities (sorted by latitude), China, October 2005–March 2016. Findings are based on 2,498,735 specimens collected from the sentinel hospitals. Normalized proportions are shown for each province and municipality as the smoothed age-specific proportions divided by the maximum smoothed proportion by lineage in the province and municipality throughout the study period to give a rescaled proxy with values between 0 (lowest proportion in the province over the study period) and 1 (highest proportion in that province over the study period).